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THE ETIOLOGY OF FIBROMYOMA OF THE UTERUS *

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The etiology of fibromyoma of the uterus has been studied from numerous angles, but we have nothing more than theories to account for the development of these tumors. The most generally accepted explanations of the pathogenesis of fibroids are Conheim's inclusion theory, upheld by Ricklinghausen, by Wolff and Müller, and by Ribbert; infection, suggested by Kolmann and by Galippi; Virchow's theory of irritation, the causes of irritation being as yet unknown; blood-vessel origin, upheld by Klebs, Gottschalk, Lubarsch, Keiffer, Pillet, and Costes—a favorite theory; and finally, the ovarian theory of Hegar, Campbell, and Seitz, who hold that disturbed internal secretion stimulates tumor growth.

Meyer,[1] in a study of the histogenesis of myoma, found total absence of vessels in numerous small myomas, and is convinced that fibroids do not arise from blood-vessel walls. He considers misplaced tissue and uterine affections with irritation highly important in the etiology.

Heimann,[2] in a study of the minute anatomy of fibroids, also found an absence of blood-vessel connection with the small tumors. In sections through sclerotic uteri without macroscopic fibroids he discovered rudimentary small tumors arising from muscle fibers.

Much stress has been placed on irritation as a factor in the pathogenesis of fibroids, yet there is a total absence of bacteriologic work in this field. It seemed to me desirable that this subject be investigated, and with the employment of a special technic it has been possible satisfactorily to proceed with such a study. Since Jan. 28, 1914, all available uterine fibroids have been examined with the object of throwing more light on the relation which infection may bear to their development.

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[1] Veit's Handb. d. Gyn., 1906, 1, p. 457.

[2] Ztsch. f. Geburtsh. u. Gynäk., 1912, 69, p. 719.

In most instances the material has been under control from the moment of opening the abdomen. This is of advantage, for it makes possible the observance of unusual care in securing uncontaminated material; also, in the interpretation of certain lesions, personal observation of the unmanipulated tissues proves to be of considerable help.

After elimination of fibromyomas undoubtedly contaminated or otherwise unsatisfactory (this necessarily excluding cultures from material from patients with recent pelvic infection), there is left a series of 80 cases.

Evidence suggestive of previous pelvic infection, old enough to merit consideration as a possible factor in the etiology of tumor growth, was found 14 times—slightly less than 18%. This is a smaller percentage of chronic pelvic infection than is ordinarily found in patients with fibromyoma.

In gross characteristics the growths revealed only such variations as we should expect to encounter in this number of cases. Histologic preparations presented no evidence of inflammatory changes. Stains for bacteria all were negative.

Disturbances elsewhere in the body, notably infections, were looked for in these patients as evidence that fibroids develop more frequently in persons with focal infections, and also for the purpose of noting whether systemic disturbances in fibromyomatous patients can be ascribed to long-drawn-out low-grade infections residing in these tumors. As would be anticipated, focal infections were often present, but no causal relation between them and the development of fibroids was evident. Systemic disturbances seemed at times out of proportion to the direct effects of pressure, hemorrhage, and other local conditions, but whether chiefly due to absorption of tumor material or in part ascribable to infectious processes, is purely conjectural. New and Wolff,[3] in an experimental and anatomic study of heart lesions in myoma cases, concluded that a specific myoma heart does not exist; the chief changes are due to anemia, but there is also a "tumor consumption heart."

TECHNIC

Skin clips with protective pads, also the resterilization of each instrument immediately after use, contributed to minimize contamination during operation. The uteri removed were at once wrapped in sterile towels, placed in the ice chest, and cultured as soon as practicable.

With all in readiness the towels were opened, the uterine surface was seared with a hot spatula, and portions of the tumors excised. Separate instruments were employed for the removal of each piece of tissue.

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[3] München. med. Wchnschr., 1912, 59, p. 72.

A sterile meat crusher, provided with a cloth covering to prevent air contamination, was used to express the fibroid juice and fine shreds of tumor tissue. This technic afforded a satisfactory asepsis and yielded much tissue extract. Similar pieces from the same locality were ground in sand by means of a pestle and mortar enclosed in a sterile cloth sack provided with a window (Rosenow). The latter procedure is not so eminently fitted for fibroid work because of the frequent toughness of the tissues.

In cases of succulent tumors, media were inoculated with the juice which exuded from the cut surfaces.

Media.—The concentrated turbid blood-stained fluid was clarified through mixture with broth or ascites broth and was then introduced into a sufficient number of culture tubes to insure moderately transparent media. Aerobic and anaerobic blood-agar slants, ascites broth, also ascites-agar shake cultures of varied reaction, some sugar-free and others containing 1% dextrose, were the most used in attempts to obtain bacterial growth. The usual variety of media were employed in subculture for purposes of identification.

RESULTS

As stated, some cases were eliminated because of obviously undesirable material or unsatisfactory technic. Eighty remained.

No growth was obtained from the fibromyomas of 45 patients.

Twenty-two more, virtually belong in the same group. A few of these contained occasional cloudlike spreading colonies of a contaminating gram-negative bacillus. A gram-negative thin bacillus, 2 to 3 microns in length, was another invader. Scattered staphylococcus colonies or surface contamination appeared in some.

Thirteen cases with positive findings were left for consideration. The detailed results obtained from them are shown in the accompanying table.

Diphtheroid bacilli were found in 3 cases (6, 9, and 11). In Case 6, there were many colonies of diphtheroid bacilli in each of several culture tubes. The material obtained from Case 9 was sufficient for only 2 shake cultures, but each contained a pure growth of half a dozen colonies. From Case 11, considerable numbers of diphtheroid bacilli and numerous colonies of staphylococci were isolated.

In one other instance (Case 1) were found many staphylococcus colonies of such type that their presence suggested infection.

Aerobic streptococci were found 3 times, in Cases 7, 12, and 13. Innumerable colonies of nonhemolyzing long-chained streptococci developed in cultures from the endometrium and from the fibroid of Case 7. This tumor was of an infiltrating type, without clearly defined capsule. In the other two instances cultures revealed only scattered colonies of nonhemolyzing streptococci, once in association with gram-positive aerobic bacilli.

Anaerobic streptococci appeared once (Case 4). From 4 to 10 colonies were present in pure growth in each of several tubes.

Gram-positive small aerobic bacilli occurred in cultures twice. In Case 6, from 1 to 3 colonies were present in each of several culture tubes. A like growth was obtained from the endometrium. In the other instance, Case 13, in addition to several colonies of this organism, aerobic streptococci were also found.

Gram-positive diplococci were found once. The material employed consisted of several small fibroids, firmly embedded in the uterine wall, and possessed of ill-defined capsules. Each of 5 culture tubes contained 1 colony of gram-positive diplococci. These failed to form chains or to reveal characteristics of staphylococci in subcultures.

Colonies of gram-positive small paired bacilli developed twice. The presence of staphylococci in the first case renders these findings less valuable. In the other case, in addition to several colonies of this organism in each culture tube, a similar, but gram-negative, bacillus also developed. The latter organism appeared in no other instance.

Bacillus welchii grew freely in cultures from 1 case. In the same set of culture tubes there developed a knobbed gram-positive anaerobic bacillus.

As seen from the table, other pelvic lesions were present in 5 cases, in 3 of which they were definitely ascribable to infectious processes. The material from 2 of these was available for grinding, but growths were not obtained.

Whenever possible, the endometrium was examined for organisms throughout the series. In 13 cases of fibroids with bacteriologic finding, an attempt was made 6 times to procure growth from the endometrium. Cultures were obtained from 2, Cases 6 and 7. In these were found the respective organisms which were present in the fibroid cultures; namely, gram-positive bacilli and nonhemolyzing streptococci.

A number of the organisms isolated were tested for virulence. Intravenous injection of rabbits and intraperitoneal inoculation of guinea-pigs failed to reveal toxic effects, and autopsies were negative. Altho fresh subcultures were always used for animals, due allowance should be made for the time the organisms were grown on laboratory media; in some instances this amounted to many days.

Inoculation of the uteri and pelvic tissues of rabbits with the isolated strains of diphtheroid bacilli and streptococci failed to produce signs of tumor growth.

ORGANISMS FOUND IN CULTURES FROM 13 CASES OF FIBROMYOMA SELECTED FROM A SERIES OF 80 CASES

Case	Staphylococcus	Diphtheroid Bacillus	Gram-positive Diplococcus	Aerobic Streptococcus	Anaerobic Streptococcus	Gram-positive Small Paired Bacillus
1	+	—	—	—	—	+
2	—	—	—	—	—	+
3	—	—	—	—	—	—
4	—	—	—	—	+	—
5	—	+	—	—	—	—
6	—	—	—	—	—	—
7	—	—	—	+	—	—
8	—	—	+	—	—	—
9	—	+	—	—	—	—
10	—	—	—	—	—	—
11	+	+	—	—	—	—
12	—	—	—	+	—	—
13	—	—	—	+	—	—
Total	2	3	2	3	1	2

SUMMARY

Attempts to secure cultures were made with selected material from 80 patients with uterine fibroids. This material consisted of juices obtained by means of a meat crusher, and by grinding.

Forty-five specimens yielded no growth and 22 more were essentially negative.

Thirteen gave positive findings. In 6 of these the endometrium was studied with positive results in 2 cases, and negative results in 4.

In 2 instances in which the patients had suffered from previous pelvic infection the diseased tissues were ground and cultured in a search for growth similar to that obtained from the fibroids. The media remained sterile.

Diphtheroid bacilli, streptococci, and small gram-positive bacilli were most often found. None of these exhibited virulence for animals. There was no tendency to produce new growth in the uteri and other pelvic organs of animals inoculated.

DISCUSSION

A causal relationship between bacterial invasion of the uterus and the development of fibroid tumors is not evident; the small percentage of cases which yielded growth, the considerable variety of the bacteria isolated, and the lack of pathogenicity for inoculated animals, permit no other deduction. These results, it may be stated, are not in accord with the impression which I have received from clinical experience.

ORGANISMS FOUND IN CULTURES FROM 13 CASES OF FIBROMYOMA SELECTED FROM A SERIES OF 80 CASES—*Continued*

Gram-positive Small Aerobic Bacillus	Gram-negative Minute Aerobic Bacillus	Bacillus Welchii	Anaerobic Gram-positive Small Bacillus	Knobbed Gram-positive Anaerobic Bacillus	Complications
—	—	—	—	—	Cyst, salpingitis, adhesions
—	+	—	—	—	
—	—	+	—	+	
—	—	—	—	—	Infected (?) edematous uterus
—	—	—	—	—	
+	—	—	—	—	
—	—	—	—	—	
—	—	—	—	—	Chronic metritis
—	—	—	—	—	Papilloma ovary
—	—	—	+	—	
—	—	—	—	—	
—	—	—	—	—	Carcinoma cervix
+	—	—	—	—	
2	1	1	1	1	

There arises another question of some interest; namely, the significance which attaches to the occurrence of growth in 13 of the 80 cases studied. It seems improbable that technical errors are responsible for the essentially pure cultures obtained, yet such a possibility must be frankly admitted. A not illogical assumption is that bacteria lie inactive in various body tissues. This is an explanation which strongly appeals to me. Tubercle bacilli may long remain dormant in the lungs; typhoid "carriers" harbor their infections for periods of years; focal infections in bones, and probably also in kidneys, in lymph glands, and in the prostate, remain indefinitely. The European war has demonstrated that infection flares up on reamputation of limbs many months after apparent healing of the old stump.

In inactive tissues such as fibroid tumors, chronically enlarged breasts, and certain other resting organs, we are not accustomed to think that bacteria remain dormant. Perhaps these tissues, poor in phagocytic cells and protective leukocytes, are not so free from bacterial invasion as has been generally assumed.